



Influence of infant microbiome on health and development

Noelle Younge, MD, MHS

Duke University School of Medicine, Durham, NC, USA

The microbiome is a complex ecosystem comprising microbes, their genomes, and the surrounding environment. The microbiome plays a critical role in early human development, including maturation of the host immune system and gastrointestinal tract. Multiple factors, including diet, antibiotic use, and other environmental exposures, influence the establishment of the microbiome during infancy. Numerous studies have identified associations between the microbiome and neonatal diseases, including necrotizing enterocolitis, sepsis, and malnutrition. Furthermore, there is compelling evidence that perturbation of the microbiome in early life can have lasting developmental effects that increase an individual's risk for immune and metabolic diseases in later life. Supplementation of the microbiome with probiotics reduces the risk of necrotizing enterocolitis and sepsis in at-risk infants. This review focuses on the structure and function of the infant microbiome, the environmental and clinical factors that influence its assembly, and its impact on infant health and development.

Key words: Microbiome, Neonate infant, Host-microbiome interaction

Key message

- The infant gut microbiome is highly dynamic and individualized.
- Microbes are vertically transmitted from mother to infant during delivery and throughout infancy.
- Delivery mode, gestational age, diet, and antibiotic use influence infant microbiome composition and function.
- In animal studies, the microbiome played critical roles in the structural and functional development of the infant gastrointestinal and immune systems.
- Microbiome-targeted therapies have great potential to reduce infant morbidity and mortality.

Introduction

After birth, the infant's skin and mucosal surfaces become

rapidly colonized by complex microbial communities of bacteria, fungi, and viruses.¹⁻³⁾ In early infancy, the composition and diversity of these microbial communities diverge by body site, driven by differences in nutrient availability, the chemical environment, and the host's immune system across sites.^{3,4)} Multiple environmental factors influence the microbiome in infancy, including the maternal microbiome, the infant's diet, delivery mode, and antibiotic exposure.^{1,5-8)} The microbiome plays a critical role in shaping multiple aspects of infant development, including the structure and function of the immune system and intestinal tract.⁹⁾ Alterations to the composition and diversity of the infant microbiome are associated with multiple morbidities including necrotizing enterocolitis (NEC), sepsis, growth failure, malnutrition, and others.¹⁰⁻¹⁴⁾ Furthermore, compelling evidence supports that alterations to the microbiome in early life have lasting effects on child development that may increase the risk of immune and metabolic diseases in later life.¹⁵⁻¹⁹⁾ This review will focus on the assembly of microbiome in infancy, its influence on infant health and development, and potential microbiome-targeted therapies to improve health outcomes.

Sources and dynamics of microbiome assembly in infancy

The sources of microbes that seed the infant's gut microbiome include strains present in the microbiomes of the mother, other caregivers, and the infant's environment.^{5,20)} A diversity of organisms from the mother's oral, vaginal, and skin microbiomes are transiently present in the early neonatal intestinal microbiome, but many are soon replaced by species better adapted to the intestinal environment (Table 1).^{3,20)} Of all maternal body sites, the fecal microbiome contributes the highest number of strains that stably colonize the infant gut.^{5,20)} Approximately half of the species present in the infant's gut microbiome are shared with the maternal microbiome.²⁰⁾ Many of these

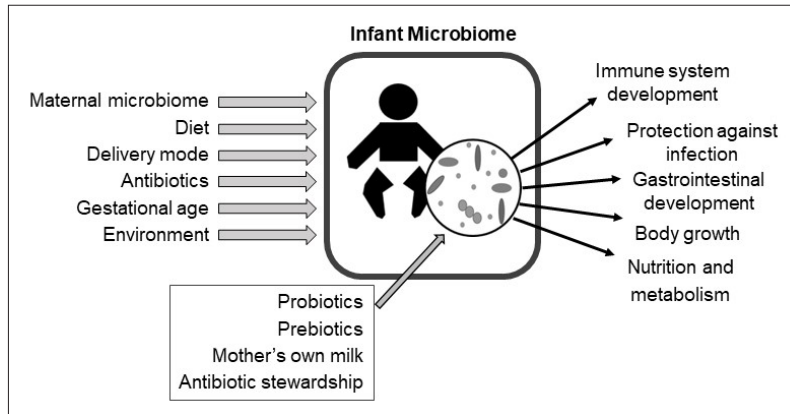
Corresponding author: Noelle Younge, MD, MHS. Duke University School of Medicine, DUMC Box 2739, Durham, North Carolina 27710, USA

✉ Email: noelle.younge@duke.edu, <https://orcid.org/0000-0001-7829-0608>

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Graphical abstract

Table 1. Vertical transmission of bacteria from the maternal microbiome to the infant gut microbiome

| Maternal body site | Contribution to the infant's fecal microbiome |
|----------------------------------|---|
| Fecal ^{1,3,5,20,22,23)} | The infant fecal microbiome shares more species and strains in common with the maternal fecal microbiome than other maternal body sites. Strains commonly shared between maternal and infant fecal microbiomes include strains of <i>Bacteroides vulgatus</i> , <i>Bacteroides uniformis</i> , <i>Parabacteroides distasonis</i> , <i>Bifidobacterium adolescentis</i> , <i>Bifidobacterium longum</i> , and <i>Escherichia coli</i> . In some cases, nondominant strains within a bacterial species in the maternal fecal microbiome are transmitted to the infant instead of the dominant strain. |
| Vagina ^{3,5,20)} | Shared species are present in the maternal vaginal microbiome and infant fecal microbiome after birth, but typically do not persist in the infant's fecal microbiome. Species shared between mothers and infants include <i>Lactobacillus</i> spp, <i>Gardnerella vaginalis</i> , and <i>Atopobium vaginae</i> . |
| Skin ^{3,20)} | A minor proportion of the infant's fecal microbiome is shared with mother's skin microbiome at birth, but these species typically do not persist in infant's fecal microbiome. |
| Oral ^{3,20)} | Shared species are transiently present in the infant fecal microbiome after birth, but typically do not persist |
| Milk ^{20,27)} | Shared <i>Bifidobacterium</i> strains and other taxa are present in mother's milk and infant fecal microbiome. Retrograde transfer of bacteria from the infant's oral cavity during breastfeeding may contribute to shared taxa in maternal and infant microbiomes. |

shared species are present at a low relative abundance in the maternal fecal microbiome, as differences in diet and the biochemical environment in the infant gut exert unique selective pressures compared to the mother.²⁰⁾ The specific bacterial features that confer a selective advantage for some strains to colonize and persist in the infant gut over others are only beginning to be elucidated, but they include genes involved in polysaccharide utilization, surface adhesion, and iron acquisition.^{21,22)} Bacterial strains within the *Bacteroides*, *Bifidobacterium*, and *Escherichia* genera are commonly shared between mothers and their infants. Infants born by cesarean delivery and infants of mothers who were administered peripartum antibiotics have a lower proportion of shared bacterial strains from the mother's microbiome than those born by vaginal delivery without maternal antibiotic exposure.^{5,6,23)} In addition to bacteria, other elements of the microbiome, including bacterial viruses (bacteriophages) and fungi, may be vertically transmitted from mothers to their infants.^{24,25)}

Human milk is another source of bacteria that may colonize the infant's intestinal tract.^{20,26,27)} Breast milk contains viable microbial communities often dominated by *Staphylococcus*, *Streptococcus*, *Acinetobacter*, and *Pseu-*

domonas.²⁶⁻²⁸⁾ While the microbial profiles of human milk and infant stool are generally distinct, there are shared bacterial groups between mother's milk and her infant's stool.^{26,27)} Elucidating the contribution of the breast milk microbiome to the infant gut microbiome has been challenging due to several factors including contamination of milk samples with maternal skin flora, retrograde transfer of the infant's oral bacteria to the mammary gland and milk during breastfeeding, and technical difficulties extracting and amplifying bacterial DNA from milk.^{27,29)} Milk from mothers who feed expressed breast milk has fewer bacterial types in common with the infant gut microbiome than that from mothers who directly breastfeed their infants, suggesting that the transfer of bacteria from the infant mouth could be a source of bacteria in mother's milk.²⁷⁾

Other sources of bacteria that seed the infant gut include microbes transmitted from other family members and microbes present in the physical environment.²³⁾ The hospital environment may serve as a reservoir of strains that colonize the infant, particularly among infants born preterm.³⁰⁻³³⁾ In fact, preterm infants often share identical bacterial strains with other infants in the neonatal intensive care unit.^{21,34)}

The assembly of the microbiome in infancy is a highly dynamic process.^{1,7,35} Meconium samples collected from infants typically contain low or undetectable amounts of bacterial DNA, but a rapid rise in bacterial density occurs within the first postnatal days.² Many of the early colonizers of the infant's intestinal tract are facultative anaerobes (e.g., *Enterococcus*, *Escherichia*, *Staphylococcus*).^{1,2,36} Over time, an increase is observed in the relative abundance of strictly anaerobic organisms. This is thought to reflect a shift from an aerobic to anaerobic environment in the intestine. However, in silico modeling of the meconium microbiome suggests that bacterial growth occurs under anaerobic conditions within hours of birth.² After this transition, *Bifidobacterium* and *Bacteroides* spp. commonly dominate the infant gut microbiome.^{1,7,37,38} In breastfeeding infants, these bacteria outcompete others secondary to their ability to digest human milk oligosaccharides (HMOs).^{37,38} In later infancy, the relative abundance of anaerobic taxa characteristic of the adult fecal microbiome increases (e.g., *Ruminococcus*, *Roseburia*).¹ While the microbiome of young breastfeeding infants is enriched in genes involved in HMO degradation, the microbiome of older infants is enriched with genes required for the digestion of dietary fibers present in solid foods.^{1,37}

Environmental factors that influence infant microbiome

The infant microbiome is highly individualized. Variation among individual infants often exceeds the variation attributable to environmental exposures and treatments.^{6,39} Environmental factors that have been consistently associated with microbiome composition and function include delivery mode, gestational age, diet, and antibiotics.

1. Delivery mode

The early microbiome of infants born by cesarean delivery differs from that of infants born by vaginal delivery.^{1,6,23,40} These differences are most apparent in the early neonatal period and diminish over time.^{1,3,6} The gut microbiome of infants born vaginally is characterized by a higher relative abundance of *Bacteroides* spp., *Bifidobacterium* spp., and *Escherichia coli*, while the microbiome of infants born by cesarean delivery has higher relative abundance of *Klebsiella*, *Enterococcus*, *Streptococcus*, and *Enterobacter* spp.^{1,5-7,39,41} Many of the taxa that are overrepresented in the gut microbiome of infants born by cesarean delivery are hospital-associated opportunistic pathogens. Cesarean delivery is also associated with a higher abundance of antibiotic resistance genes in the neonatal microbiome.¹ Some studies demonstrated that the differ-

ences in the composition of the microbiome of infants born by cesarean versus vaginal delivery are associated with functional changes that may impact immune system development.^{40,42,43} For example, one study reported an enrichment of lipopolysaccharide (LPS) biosynthesis pathways in the microbiomes of infants born vaginally.⁴² LPS extracts from stool samples of vaginally delivered infants induced stronger proinflammatory cytokine responses in vitro compared to samples from infants born by cesarean delivery. Studies support that maternal-to-infant transmission of bacterial strains continues to occur throughout infancy and the composition of the microbiome of infants born by cesarean delivery becomes increasingly similar to that of infants born by vaginal delivery over time.^{3,21}

2. Gestational age

Gestational age strongly influences the development of the gut microbiome in infancy. Compared to the microbiome of term infants, the microbiome of preterm infants is characterized by low bacterial diversity, increased relative abundance of *Enterobacteriaceae* (e.g., *Klebsiella*, *Enterobacter*), a paucity of *Bifidobacterium*, and enrichment of antibiotic resistance genes.^{4,39,44-46} The gut microbiome of preterm infants is often dominated by only a few bacterial species.⁴⁷ The altered development of the microbiome of preterm versus full-term infants is likely due to a number of factors including frequent antibiotic exposure, the neonatal intensive care unit environment, delays and interruptions in the establishment of enteral feedings, and immaturity of the gut and immune system. In contrast to full-term infants, birth mode does not appear to have a strong influence on the microbiome of preterm infants.^{36,44,45}

The composition of the preterm infant microbiome also varies by postmenstrual age (PMA; birth gestational age plus chronologic age). At an early PMA, the microbiome of preterm infants is dominated by *Staphylococcus* and *Enterococcus*, followed by a transition to dominance by *Enterobacteriaceae* (e.g., *Klebsiella*, *Escherichia*), followed by an increase in the abundance of *Clostridium*, *Veillonella*, and other anaerobes and a late emergence of *Bifidobacterium*.^{12,13,35,45} This predictable progression suggests that host developmental processes influence the assembly of gut microbial communities. For example, postnatal maturation of bile acid synthesis and the enterohepatic cycle contributes to the development of the intestinal microbiome in neonatal mice.⁴⁸ Interactions between microbes also contribute to the microbiome development in preterm infants. For example, inhibitory interactions between *Klebsiella*, *Enterococcus*, *Staphylococcus*, and *Candida* may drive the ordered succession of these organisms in the preterm infant gut.³⁶

3. Antibiotics

Antibiotics disrupt the richness, diversity, and stability of the infant microbiome.^{37,44,49,50} In preterm infants, antibiotic use is associated with enrichment of antibiotic resistance genes in the microbiome and disruption of multiple functional metabolic pathways including short-chain fatty acid production.^{44,51} Maternal antibiotic exposure may also influence the infant's microbiome. For example, intrapartum antibiotic administration is associated with lower bacterial diversity, a lower relative abundance of *Bifidobacteriaceae*, and an increased relative abundance of *Proteobacteria* in the exposed versus unexposed infant's intestinal microbiome.⁵²

4. Diet

Diet has strong influence on the infant microbiome.^{1,7} Human milk contains multiple bioactive factors that influence the microbiome, including immunoglobulins and HMOs.^{53,54} HMOs are abundant structurally diverse sugar chains in human milk. HMOs are indigestible by the infant and reach the lower intestinal tract intact. *Bifidobacterium* and *Bacteroides* encode the enzymes necessary to break down HMOs and generally become the most abundant bacterial genera in the infant microbiome. While exclusively breastfed infants have lower diversity and higher relative abundances of certain *Bifidobacterium* and *Lactobacillus* spp., nonexclusively breastfed infants have higher relative abundances of other taxa including *Bacteroides* and *Eubacterium*.^{1,7,55} In one study, even brief formula supplementation among otherwise exclusively breastfed infants during the postnatal hospitalization was associated with lower relative abundance of *Bifidobacteriaceae* at 3–4 months of age compared to exclusively breastfed infants not exposed to supplemental formula.⁵⁵

Formula type may also influence the microbiome. For example, the microbiomes of infants fed soy formula or lactose-reduced formula supplemented with corn syrup solids have increased relative abundance of *Lachnospiraceae*.^{8,56} Preterm infants who are fed pasteurized donor human milk have altered microbiome profiles compared to those fed their mother's own milk, including a lower relative abundance of *Bifidobacteriaceae*.^{57,58} Diet also affects the metabolic capacity of the gut microbiome. For example, the microbiomes of breastfed versus formula-fed infants are enriched in multiple amino acid synthesis pathways.⁸ In later infancy, the cessation of breastfeeding is associated with a shift toward an adult-like composition including increased abundance of *Roseburia*, *Bilophila*, *Clostridium*, *Bacteroides*, and *Anaerostipes* as well as an enrichment of the genes required for fiber degradation.¹

Beneficial effects of microbiome on infant development

The microbiome has a broad range of effects on infant development, including roles in immunity, growth, metabolism, and neurodevelopment.^{9,59–63} These effects occur through direct interactions of the microbiome with the host's immune system at the skin and mucosal interfaces as well as through the production of bioactive metabolites by the microbiome that are absorbed into the circulation.^{19,61,63,64} The infant's immune system and gastrointestinal tract develop upon close interaction with the microbiome. Evidence from studies of germ-free animals reared in a sterile environment demonstrated the importance of the microbiome for normal intestinal and immune development. Germ-free rodents have enlarged ceca, reduced gastrointestinal motility, altered intestinal epithelial cell morphology including longer villi and shorter crypts, and structural and functional deficits in immune development.^{9,65–67} Multiple studies reported a sensitive period in early life during which certain aspects of immune development are uniquely influenced by the microbiome, and perturbations of the microbiome during this period may have lasting health consequences.^{16,18,19,68,69} Similarly, metabolic programming is uniquely influenced by the microbiome during early life, and disruption of the maternal and infant microbiomes may increase an individual's susceptibility to later metabolic diseases including obesity.^{15,17,70,71}

The codevelopment of the microbiome, gastrointestinal tract, and immune system also influence physical growth in infancy. Young germ-free mice demonstrate slower weight gain, length gain, organ and bone growth as well as greater weight loss during periods of malnutrition than mice raised with a conventional microbiome, demonstrating the importance of the microbiome for supporting early life growth.⁶⁰ Germ-free mice have lower circulating levels of insulin-like growth factor 1 (IGF-1) and growth hormone sensitivity in the peripheral tissues than those raised with a microbiome.⁶⁰ In a mouse model of malnutrition, a select *Lactobacillus plantarum* strain was sufficient to increase IGF-1 production and sustain postnatal growth through a mechanism involving the interaction between its cell wall components and the pattern recognition receptor nucleotide-binding oligomerization domain-containing-2 in the intestinal epithelium.⁶¹ In human infants and children, malnutrition is associated with persistent immaturity in the intestinal microbiome.¹⁴ Transferring fecal bacteria from children with malnutrition to germ-free mice recapitulates phenotypic features of malnutrition in the animals, supporting a causal role of the microbiome in malnutrition.⁵⁹ A dietary intervention designed to modulate the microbiome of children with malnutrition to a composition similar to

Table 2. Studies of probiotics for neonatal diseases^{a)}

| Study | Description | No. of studies and infants | Results for effect of probiotic and/or synbiotic treatment vs. control |
|---|--|---|---|
| Systematic reviews and meta-analyses | | | |
| Sharif et al. ⁸²⁾ 2020 | Included RCTs and quasi-RCTs of probiotics for infants born <32 weeks' gestation and/or <1,500 g | 56 Trials with 10,812 infants | NEC: RR, 0.54; 95% CI, 0.45–0.65 Mortality: RR, 0.76; 95% CI, 0.65–0.89 Late-onset invasive infection: RR, 0.89; 95% CI, 0.82–0.97 |
| Dermyshe et al. ⁸⁰⁾ 2017 | Included RCTs and observational studies of probiotics for infants born <34 weeks' gestation and <1,500 g | 30 Trials with 8,622 infants and 14 observational studies with 13,779 infants | Severe NEC: RR, 0.57; 95% CI, 0.47–0.70 in RCTs, RR, 0.51; 95% CI, 0.37–0.70 in observational studies All-cause mortality: RR, 0.77; 95% CI, 0.65–0.92 in RCTs, RR, 0.71; 95% CI, 0.62–0.81 in observational studies Late-onset sepsis: RR, 0.88; 95% CI, 0.80–0.97 in RCTs, RR, 0.81; 95% CI, 0.69–0.96 in observational studies |
| Sawh et al. ⁸¹⁾ 2016 | Included RCTs of probiotics for infants born <37 weeks' gestation and/or <2,500 g | 42 Trials with 10,520 infants | Severe NEC: RR, 0.53; 95% CI, 0.42–0.66 All-cause mortality: RR, 0.79; 95% CI, 0.68–0.93 Culture-proven sepsis RR, 0.88; 95% CI, 0.77–1.00 |
| Rao et al. ⁸⁶⁾ 2016 | Included RCTs of probiotics for infants born <37 weeks' gestation and/or <2,500 g | 37 Trials with 9,416 infants | Late-onset sepsis: RR, 0.86; 95% CI, 0.78–0.94 |
| Large randomized, controlled trials | | | |
| Costeloe et al. ⁸⁷⁾ 2016 | RCT of probiotics (<i>Bifidobacterium breve</i>) for infants born 23–30 weeks' gestation | 1,315 Infants | Late-onset sepsis: RR, 0.97; 95% CI, 0.73–1.29 NEC ≥stage 2: RR, 0.93; 95% CI, 0.68–1.27 Mortality: RR, 0.93; 95% CI, 0.67–1.30 |
| Jacobs et al. ⁸⁸⁾ 2013 | RCT of probiotics (<i>Bifidobacterium infantis</i> , <i>Streptococcus thermophilus</i> , and <i>Bifidobacterium lactis</i>) for infants born <32 weeks' gestation and <1,500 g | 1,099 Infants | Late-onset sepsis: RR, 0.81, 95% CI, 0.61–1.08 NEC: RR, 0.46, 95% CI, 0.23–0.93 Mortality: RR, 0.97, 95% CI, 0.58–1.62 |
| Panigrahi et al. ⁸⁵⁾ 2017 | RCT of synbiotic (<i>Lactobacillus plantarum</i> plus fructooligosaccharide) for infants born ≥35 weeks and ≥2,000 g | 4,556 Infants | Sepsis and death: RR, 0.60; 95% CI, 0.48–0.74 Culture-positive sepsis: RR, 0.22; 95% CI, 0.09–0.53 Culture-negative sepsis: RR, 0.53; 95% CI, 0.30–0.92 Lower-respiratory tract infection: RR, 0.66; 95% CI, 0.51–0.88 |

RCT, randomized controlled trial; NEC, necrotizing enterocolitis; RR, relative risk; CI, confidence interval.

^{a)}Table includes a selection of relevant studies; not all published studies are included.

that of healthy children improves growth and nutritional biomarkers, demonstrating the potential ability of microbiome-targeted therapies to improve growth and nutrition in early life.⁷²⁾

The commensal gut microbiome excludes pathogens from the gut and protects the host from infection through a phenomenon known as colonization resistance. There are multiple mechanisms of colonization resistance, including outcompeting pathogens for space and nutrients, bacterial secretion of antimicrobial peptides, and stimulation of the host immune system.⁷³⁾ The relatively low bacterial diversity and increased luminal oxygen availability in the neonatal gut may impair the colonization resistance of the neonatal microbiome and increase susceptibility to pathogen invasion and sepsis.^{74–76)} Colonization resistance may be further impaired following disruption of the microbiome by antibiotic use.⁷⁴⁾

Microbiome-targeted therapies to improve infant health

Given the importance of the microbiome to infant health, there is high interest in understanding the best practices to support healthy microbiome development. Antimicrobial

stewardship and breastfeeding support are sample practices that optimize the microbiome and improve infant health. Other microbiome-targeted interventions may include the administration of live bacteria (probiotics) or select nutrients that promote the growth of beneficial bacteria (prebiotics). Microbiome-targeted therapies have proven effective at reducing the incidence of NEC and sepsis, major causes of morbidity and mortality in infants (Table 2).

While the pathogenesis of NEC is not fully understood, interactions between an abnormal microbiome with the immature gut and immune system of preterm infants are central to its pathogenesis. Prolonged antibiotic use is associated with an increased risk of NEC, while breastfeeding is protective.^{77,78)} Breastmilk contains multiple bioactive components including HMOs and immunoglobulin A that likely contribute to its protective effects against NEC.^{53,79)} NEC is commonly preceded by a bloom in the relative abundance of Proteobacteria in the fecal microbiome.¹⁰⁾ Meta-analyses of randomized trials support that probiotics significantly reduce the risk of NEC and mortality in preterm infants (Table 2).^{80–82)} Further, observational studies support the effectiveness of probiotics in clinical practice.^{83,84)}

Sepsis is a major cause of morbidity and mortality in both full-term and preterm infants. A randomized controlled trial

of an oral probiotic and prebiotic preparation (*Lactobacillus plantarum* plus fructooligosaccharide) in 4,556 term infants in rural India showed a striking reduction in the primary outcome of sepsis and death in the treatment arm.⁸⁵⁾ The risk of lower-respiratory tract infections was also reduced among infants in the treatment group. Probiotics have been shown to reduce the risk of late-onset sepsis in preterm infants.⁸⁶⁾ These studies demonstrate the promise of microbiome-targeted therapies to reduce infant morbidity and mortality rates.

Conclusion

The microbiome has a key role in health and development during infancy. Its composition and function are influenced by environmental exposures throughout infancy. Interventions to promote healthy microbiome development have already proven effective for multiple diseases that affect infants, but the discovery of other means to optimize microbiome development in early life has great potential to improve health outcomes across the lifespan.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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ORCID:

Noelle Younge  <https://orcid.org/0000-0001-7829-0608>

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